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Is a Synaptic Dysfunction the Origin of Autism?

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Abstract

Autism in childhood is a heterogeneous disease with around 110 phenotypes. Around 800 genes are affiliated with autism including members of neuro-ligand, neurexin, cadherin, GABA receptors, SHANK gene families, mutated UBE3 A on chromosome 15 and SNORD 116 precursor interaction. A predominant 4:1 male to female ratio is found in autistic spectrum disorder. 50 per cent of all autistic children show chromosome deletions and duplications, these are often found on the 15th and 16th chromosome. Copy number repeat variants in DNA are also well described in pathogenesis of autism patients. There is an overlap with other neurodevelopmental syndromes like tuberous sclerosis, Williams-syndrome, Phelan McDermid syndrome and Sphrintzen syndrome. The hypothesis of the term "atypical connectivity" in different brain regions with partial under- and overconnectivity with reduced brain networking at the psychosocial level was described. Different hypothesis about the origin of autism in children were described. The hypothesis of early lack of basic trust, mercury intoxication and different aspects concerning the origin of this extraordinary disease of 2 percent of children were stated but not confirmed to date. Especially low immature production of IgF-1 by oligodendrocytes in the corpus callosum leads to slowing of the PI3K/AKT chain activation of myelination that Ig-F1 could play an important role in the origin of the disease. Synaptic dysfunction with hypomyelination and impaired impulse transmission seem to play an extraordinary role with under- and overconnectivity with reduced brain networking at the psychosocial level in autistic children. Functional underconnectivity is found in 5 different brain areas, prefrontal, parieto-occipital, motor, somatosensory and the temporal region. Functional overconnectivity is often present in temporo-thalamic regions. Recent research shed light on synaptic dysfunctions with disrupted normal impulse signaling. In this review the different neurochemical findings and the correlation of synaptic dysfunction in autistic children will be closely evaluated.

Keywords: Autism-Child-Synapsis-Atypical; Connectivity-Synaptopathy; Childhood; Autism; Central nervous system

Introduction:

Autism, differentiated in early childhood autism, autistic disorder, Asperger syndrome and atypical forms, is a profound developmental disorder that is based on complex disorders of the central nervous system, especially in the area of perception processing, and begins in childhood. At its core is a severe disorder of relationships and communication. The effects of

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the disorder hinder relationships with the environment in various ways, participation in community life, and the ability to integrate into society, as both cognitive and language, motor, emotional, and interactional functions are affected. In addition, numerous behavioral abnormalities, which can be particularly burdensome for caregivers in everyday interactions with autistic individuals, are present. Autistic individuals are typically multiply disabled. As with all multiple disabilities, the focus of the disability shifts over the course of development with age. In the international classification of diseases of the World Health Organization, the following characteristics are listed as defining features of early childhood autism, in addition to the early onset. Qualitative impairments in interpersonal relationships; impairments in communication and imagination; a significantly restricted repertoire of activities and interests. Children with autism may initially not understand gestures, smiles, or words. They are unable to establish a normal relationship with other people, even with their own parents. They withdraw, isolate themselves autistically.

Any change in their environment can greatly upset them. Children with autism cannot play "normally" and use their toys in the same, often misappropriate way. They develop stereotypes: spinning and twirling wheels, sifting sand, waving threads or paper. The main symptoms of autistic disorder vary in their severity. People with autism often have problems with eating and sleeping from infancy and develop self-stimulating behaviors that can range from self-injury to severe external aggression. They often insist on very specific orders or can drive their caregivers to despair through excessive collecting of certain objects, refusal to wear certain clothing, repetition of the same behaviors or verbal expressions. Many have no sense of danger. A large proportion of autistic individuals do not learn to speak. The intellectual abilities of people with autism vary greatly. They range from intellectual disability to normal intelligence, with some of them showing remarkable partial achievements in mathematics, technical disciplines, music, and other areas. According to current knowledge, there are 5-15 people with autistic disorders per 10,000 individuals in the population in Germany. Boys are affected by the disorder three to four times more often than girls. Early childhood autism can be found in families of all nationalities and social classes. Despite extensive research results, there is still no explanatory model that can fully and conclusively demonstrate the causes of autistic disorder. According to current knowledge, autism is not curable. As diverse as the manifestations of autistic disorder are, the pedagogical and therapeutic approaches must be equally diverse and tailored to each individual with autism. Through targeted autism-specific support and therapy measures, a significant improvement in symptoms can be achieved in many cases, increasing the quality of life for both the autistic individual and their caregivers. Recent research has highlighted the origin of autistic disorders as a synaptopathy, where excitatory synapses are more prominent than inhibitory synapses. The exact mechanism on synaptical function and formation is to date not completely understood.

The Role of Synaptic Transmission in Autistic Disorders

Physiology of Synapses

Synapse refers to the site of a neuronal connection through which a nerve cell is in contact with another cell - a sensory cell, muscle cell, gland cell, or another nerve cell. Synapses serve the transmission of excitation, but also allow the modulation of signal transmission, and they are capable of storing information through adaptive changes. The number of synapses in the brain of an adult is approximately 100 trillion (10^14) - in terms of a single neuron, it ranges between 1 and 200,000. The term synapse was coined in 1897 by Charles S. Sherrington for the connection between neurons, for example between the branched end of the axon of a nerve cell and the branched dendrites of another nerve cell. In most cases, they are chemical synapses. In these synapses, the signal that arrives as an electrical action potential is converted into a chemical signal, carried in this form across the synaptic cleft between the cells, and then transformed back into an electrical signal. The sending cell (presynaptic) releases neurotransmitters, chemical messengers, which bind to membrane receptors of the receiving cell on the other side of the cleft. This anatomically determines the direction of signal transmission (only forward), which is fundamental for information processing in neuronal networks. The excitatory transmitter is either produced in the axon terminal of the sending neuron or synthesized in its cell body and transported axonally to the presynaptic membrane regions. In contrast, electrical synapses are gap junctions, contact points where ion channels of two cells are directly coupled, allowing the passage of ions and small molecules from one cell to another. Initially, such synapses were discovered between neurons, but similar contact points are also found in other tissues, including plants. In a figurative sense, immunological synapses refer to the sites of temporary cellular contacts between cells of the immune system, both among themselves and with cells of the surrounding tissue. Molecules on the surface of one cell bind to receptor molecules and adhesion molecules in the cell membrane of the other, exchanging information. In a synaptic end bulb, the incoming action potential, during the depolarization phase - in addition to the transient opening of sodium and slightly delayed potassium ion channels - leads to the temporary opening of voltage-gated calcium ion channels and thus a brief influx of calcium ions. The increased intracellular calcium causes the release of a neurotransmitter into the synaptic cleft within a few milliseconds. In the end bulb, this neurotransmitter is stored in special synaptic vesicles and provided near the cell membrane

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in synaptic vesicles, which can fuse with the presynaptic membrane under the influence of calcium and then release the transmitter molecules outward. This process, also called exocytosis, is made possible by the conformational change of calcium-binding proteins, especially synaptotagmins. They initiate the formation of a protein complex of SNARE proteins - from a synaptobrevin in the vesicle membrane on one hand and on the other hand a syntaxin and two SNAP proteins in the cell membrane - which allows the fusion of both membranes. Other proteins are then involved in causing the fused vesicle to open outward and, for example, accelerate the release of neurotransmitters, such as Complexin I and II. Subsequently, a certain number of synaptic vesicles are provided at the axolemma again via synapsin. On the other side of the synaptic cleft, specific receptor molecules for the neurotransmitter are found in the postsynaptic, subsynaptic, membrane of the target cell. These receptors are usually associated with ligand-gated ion channels (ionotropic), so that an ion channel can open immediately when the transmitter molecule binds to the appropriate receptor. Depending on the type of ion for which this channel is permeable, the membrane potential in the postsynaptic region is either raised (EPSP) or lowered (IPSP) by the ion current. Depending on the receptor type, an indirect second messenger cascade can also be triggered (metabotropic), which can also lead to a change in membrane potential and possibly trigger further processes in the postsynaptic cell. Through the respective intracellular messenger, signal amplification can also be induced, but with a delayed effect. The transmitter molecules do not bind irreversibly but detach from their receptor after a certain time. In the synaptic cleft or extracellular space, they are often broken down by specific enzymes (such as acetylcholinesterase), limiting their effect. For some transmitters, there is no breakdown, but they are taken back into the presynaptic terminal (e.g., serotonin) or cleared by glial cells. The signals transmitted through chemical synapses have a biochemically defined effect. Depending on the equipment of the postsynaptic membrane influenced by the sending neuron, either an excitatory or inhibitory effect is achieved. Not only individual synapses, but entire neurons are therefore classified into excitatory and inhibitory, depending on whether they form only excitatory or only inhibitory synapses on target cells. For a target cell within the central nervous system, it is usually the case that it receives signals from different neurons, including opposing ones, and that the electrical voltage changes they trigger add up. If the sum of the incoming excitatory and inhibitory (postsynaptic) voltage changes at the axon hillock of this nerve cell exceeds a certain threshold during the potential change, the cell itself becomes active, generates an action potential, and transmits it further along its axon. In a variety of psychiatric and neurological disorders, it is assumed that synaptic transmission pathways are disrupted. There are indications of a link between various forms of depression and disturbances in signal transmission through the neurotransmitter serotonin. Numerous medications or toxins exert their effects by interacting with steps of transmission at synapses (beta-blockers, nicotine, atropine, hyoscyamine, parathion, cocaine, and many more). The majority of synapses operate with chemical information transmission, but in some cases, there is also direct electrical conduction. In these electrical synapses, the action potential is passed directly to the next cell without intermediary neurotransmitters. In many electrical synapses, there are connection channels through the cell membrane, called "gap junctions," through which the intracellular spaces of adjacent cells are directly coupled. These gap junctions are pores in the cell membrane formed by specific proteins called connexins. Six connexin molecules line the pore of a cell, together forming a connexon. Contact between two connexons of neighboring cells creates a channel that crosses both membranes and connects them. The open connection allows diffusion of even medium-sized molecules, such as secondary messengers, and enables a very rapid transmission of changes in membrane potential with relatively low electrical resistance through ion passages. Such electrical synapses occur, for example, between neurons in the retina; they are also found between glial cells and especially between cells of the heart muscle, allowing them to act synchronously as a single unit electrically, similar to smooth muscle like the uterus. Another form of electrical excitation transmission is capacitive coupling through a large, close membrane contact, as found, for example, in the human ciliary ganglion. Overall, excitatory and inhibitory synapses could play an important role in the origin of autism in children.

Synaptogenesis

Synaptogenesis is the formation of synapses between neurons in the nervous system, with a surge in synapse formation during early brain development. It is crucial during the critical period for neural growth and synaptic pruning. The neuromuscular junction (NMJ) is a well-studied synapse composed of a motor neuron, myofiber, and Schwann cell. The motor neuron releases acetylcholine to trigger muscle contraction. Astrocytes play a role in synapse plasticity. During development, myoblasts, motoneurons, and Schwann cells originate from different embryonic regions. Axons are guided by growth cones to form contacts with myotubes. Synapse development at the NMJ shows specific patterning with midpoints being innervated. Post-synaptic differentiation involves increased AChR concentration through clustering and gene regulation. Pre-synaptic differentiation involves changes in synaptic volume and vesicle clustering. Synaptic maturation involves synapse elimination, where multiple inputs are reduced to one. Synapse formation specificity distinguishes between fast and slow-twitch muscle fibers. In the CNS, synaptogenesis shares similarities with the

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NMJ but involves different neurotransmitters and receptors. Factors regulating CNS synaptogenesis include signaling molecules, morphology, and environmental enrichment. The Wnt protein family contributes to synapse formation in the CNS and NMJ. In the CNS, Wnts induce presynaptic and postsynaptic terminal formation in various neuronal cell types. In the NMJ, Wnts play a role in AChR clustering and growth cone enlargement. Wnt expression is essential for synaptic development and plasticity in both systems.

Post-synaptic Differentiation

Following contact with the motoneuron, the myotube shows an increased concentration of AChR in the synapse, enhancing synaptic signal transmission. This is achieved through clustering of AChR, up-regulation of AChR gene transcription in post- synaptic nuclei, and down-regulation in non-synaptic nuclei. The initiation of post-synaptic differentiation may be triggered by neurotransmitters or changes in the extracellular matrix.

Clustering

AChR multimerization in the post-synaptic membrane is facilitated by Agrin, released by the motoneuron axon. Agrin binds to MuSK receptor, activating Rapsyn, which promotes AChR clustering in the membrane.

Synapse-specific Transcription

Axonal signals regulate gene expression in myonuclei beneath the synapse, leading to localized up-regulation of AChR gene transcription. CGRP and neuregulin released by the axon activate kinases that enhance AChR gene transcription.

Extrasynaptic Repression

Activity-dependent repression of AChR gene in non-synaptic nuclei occurs due to the electrical signal generated by the synapse. This ensures AChR localization to the synapse, enhancing signal fidelity.

Pre-synaptic Differentiation

Changes in the developing axon terminal include increased synaptic volume, vesicle clustering, and membrane polarization. Neurotrophins and cell adhesion molecules released from muscle cells mediate these changes.

Synaptic Maturation

Synapses segregate as they mature, with all axonal inputs except one retracting. The post-synaptic end plate deepens and forms folds to increase neurotransmitter reception. Schwann cells transition from loose covers to myelinated caps over the neuromuscular junction.

Synapse Elimination

Synaptic pruning involves competition between axons, with stronger synapses maintained through synaptotrophins and weaker ones eliminated. Synaptotoxins released from depolarized post-synaptic membranes deter weaker axons.

Synapse Formation Specificity

Motoneurons distinguish between fast and slow-twitch muscle fibers through selective or non-selective pathways. Axons recognize fiber types or are guided by predetermined paths to innervate specific muscle fibers.

Central Nervous System Synapse Formation

Similarities exist between NMJ and CNS synapses in structure and function. Both exhibit pre- and post-synaptic membrane differentiation, receptor clustering, and synapse elimination. However, CNS synapses involve different neurotransmitters and receptors and exhibit greater complexity due to multiple inputs and neuronal plasticity.

Different Neurochemical Findings in Autistic Setting

Different neurochemical findings were found in autistic children and evaluated in detail in former studies concerning finding the origin of autism.

Increase of excitatory and decrease of inhibitory synapses: In autism, there is an increase in excitatory synapses and a decrease in inhibitory synapses in the prefrontal cortex (37,42). Previous research has shown that there are more excitatory pyramidal cells and fewer inhibitory parvalbumin+ chandelier interneurons in the prefrontal cortex of individuals with autism (37,42,46). The overall impact of these changes on synaptic abundance in the cortex remains unclear. In a recent study, researchers examined the number of excitatory and inhibitory synapses in the prefrontal cortex of 10 postmortem brains from individuals with autism and 10 control cases (37,42,46). Excitatory synapses were identified using VGlut1 and postsynaptic density protein-95 markers, while inhibitory synapses were identified using vesicular gamma-aminobutyric acid transporter and gephyrin markers. The analysis revealed an increase in excitatory synapses in upper cortical layers and a decrease in inhibitory synapses across all cortical layers in autism brains compared to controls (37,42,46). These alterations in synaptic numbers may contribute to neuronal dysfunction and disrupted network connectivity in the prefrontal cortex of individuals with autism (37,42,46).

Low IgF-1 Production in oligodendrocytes in the Corpus Callosum*:*

Slowing of PI3K/AKT chain activation of myelinisation; early prevention of autism could be achieved by measuring IgF-1 in umbilical cord blood at delivery (52). This leads to synaptic dysfunction with hypomyelinisation and disturbed impulses (52).

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Loss of Protein Tyrosine Phospatase Receptor Delta (Ptprd): The brain cortex plays a crucial role in higher-level cognitive functions, and disruptions during cortical development can lead to lasting consequences and are linked to brain disorders (39). Previous research has shown that the protein tyrosine phosphatase receptor delta (Ptprd), associated with various neurodevelopmental disorders, is vital for cortical brain development (39). Loss of Ptprd expression results in an abnormal increase in excitatory neurons in mice by overactivating pro-neurogenic receptors TrkB and PDGFRβ in neural precursor cells (39). A recent study aimed to investigate the long-term effects of these alterations in adulthood (39). This study revealed that in Ptprd+/- or Ptprd-/- mice, the excessive excitatory neurons persisted into adulthood, impacting excitatory synaptic function in the medial prefrontal cortex (39). Ptprd heterozygosity or homozygosity led to an increase in inhibitory GABAergic neurons in the cortex and impaired inhibitory synaptic transmission (39). Furthermore, Ptprd+/- or Ptprd-/- mice exhibited autistic-like behaviors without learning and memory deficits or anxiety (39). The findings suggest that the loss of Ptprd has enduring effects on cortical neuron numbers and synaptic function, potentially influencing ASD-like behaviors (39).

Mutation of Neuroligin-3-R451C: The gut's intrinsic nervous system interacts with gut-associated lymphoid tissue (GALT) through neuroimmune interactions. The caecum, a crucial region of the gastrointestinal tract, plays a role in immune responses and microbial regulation. Individuals with Autism Spectrum Disorder (ASD) often experience gastrointestinal issues, including inflammatory disorders. Mutations in genes like neuroligin-3 (NL3) are linked to autism and synaptic transmission impairments. NL3R451C mice, a model of autism, show altered enteric neurons and GI dysfunction. Researchers investigated the impact of the R451C mutation on the caecal nervous system and immune function (53). NL3R451C mice had reduced caecal weight and increased neuron density, particularly NO- producing neurons (53). The density of Iba-1 labeled macrophages in the caecal patch was higher in NL3R451C mice, with smaller and more spherical morphology. These findings highlight the effects of the autism-associated Nlgn3 mutation on neural and immune pathways. (53-55).

Reduced number of Chandelier cells: Chandelier (Ch) cells are a type of cortical interneuron characterized by axon terminal structures called cartridges that form synapses on the axon initial segment of excitatory pyramidal neurons. Previous research suggests that individuals with autism have a lower number of Ch cells and reduced GABA receptors in the Ch cell synaptic targets in the prefrontal cortex (41). To further investigate Ch cell alterations, researchers compared the length of cartridges and the number, density, and size of Ch cell synaptic boutons in the prefrontal cortex of individuals with autism and control subjects and analyzed postmortem samples of the human prefrontal cortex (Brodmann Areas 9, 46, and 47) from 20 individuals with autism and 20 age- and sex-matched controls (41). Ch cells were identified using an antibody against parvalbumin, a marker that labels soma, cartridges, and synaptic boutons. The results showed no significant differences in the average length of cartridges or the total number or density of boutons between control subjects and those with autism. Researchers observed a significant decrease in the size of Ch cell boutons in individuals with autism. This reduction in bouton size may lead to decreased inhibitory signal transmission and affect the balance of excitation to inhibition in the prefrontal cortex in autism (41).

Microglial Tmem59-Deficiency: Synaptic abnormalities are a key feature of autism spectrum disorders and contribute to behavioral issues in these disorders. Microglia, the brain's immune cells, are involved in synapse refinement. Dysregulated synaptic pruning by microglia during brain development has been linked to ASDs, but the exact mechanism is not fully understood. We found that the expression of Transmembrane protein 59 (TMEM59), which regulates microglial function, is reduced in autistic patients (43). Mice lacking TMEM59, either completely or specifically in microglia, displayed ASD-like behaviors (43). These mice also showed increased excitatory synaptic transmission, dendritic spine density, and levels of excitatory synaptic proteins (43). TMEM59-deficient microglia had impaired synapse engulfment ability both in vivo and in vitro.

Researchers from China discovered that TMEM59 interacts with the C1q receptor CD93, and TMEM59 deficiency leads to CD93 protein degradation in microglia, impairing synapse engulfment (43). This study highlights the role of TMEM59 in regulating microglial function in synapse refinement during brain development and suggests that TMEM59 deficiency may contribute to ASDs by disrupting synapse phagocytosis and altering neuronal activity balance (43).

CHD8-gene loss on genome organization: Whole-exome sequencing of individuals with autism spectrum disorder (ASD) and their unaffected family members has identified CHD8 as a frequently mutated gene (44). However, the impact of CHD8 loss on genome organization and neuronal function remains poorly understood. In a recent study, researchers generated human embryonic stem cell lines with CHD8 mutations and observed altered gene expression in differentiated cortical neurons, particularly affecting neural development and synaptic transmission (44). CHD8+/- neurons exhibited reduced firing rates and synaptic activity, which could be rescued by CHD8 overexpression. Additionally, CHD8+/- neurons showed increased chromatin accessibility, particularly near the AUTS2 gene implicated

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in ASD. The genes affected in CHD8+/- neurons overlap with those mutated in ASD, intellectual disability, and schizophrenia, highlighting the potential role of CHD8 in these disorders. The study provided insights into the molecular and functional consequences of CHD8 mutations in neurons (44).

Defects in syntabulin-mediated synaptic cargo transport: The formation and maintenance of synapses rely on the delivery of synaptic proteins from the soma to distal synapses. Impaired transport may be linked to neurodevelopmental disorders like autism (45). Syntabulin acts as a motor adapter for kinesin-1 and presynaptic cargos (45). Defects in syntabulin- mediated transport lead to reduced synapse formation and maturation, contributing to autism-like synaptic dysfunction and social behavioral abnormalities (45). Syntabulin expression peaks in early postnatal development and declines with brain maturation. Neurons lacking syntabulin show impaired transport, reduced synapse density, altered synaptic transmission, and behavioral abnormalities resembling autism traits. A human missense variant of syntabulin found in an autism patient fails to rescue synaptic deficits in mice lacking syntabulin (45). This important study suggests that impaired transport mechanisms contribute to synaptic dysfunction and behavioral abnormalities in autism (45).

Changes in metabotropic glutamate receptor (mGluR) signaling*:* Various neurodevelopmental disorders are associated with changes in metabotropic glutamate receptor (mGluR) signaling, which plays a crucial role in synaptic plasticity, spine maturation, and circuit development. In one study published in Nature Communications in 2019, Edfawy et al. explored the function of Gprasp2, a gene implicated in neurodevelopmental disorders that is involved in sorting G-protein- coupled receptors after endocytosis (47). Deleting Gprasp2 in mice results in ASD-like behavior and synaptic communication alterations (47). Modulating Gprasp2 levels affects mGluR5 surface availability, impacting dendritic complexity, spine density, and synaptic maturation bidirectionally (47). Gprasp2 loss enhances hippocampal long-term depression, indicating increased mGluR-dependent activation. These findings highlight Gprasp2's role in glutamatergic synapses and provide insights into its association with neurodevelopmental disorders (47).

KMT5B deficiency in prefrontal cortex: Large-scale genetic screening has identified KMT5B (SUV420H1) as a high-risk gene for autism due to its role as a histone (48). H4 K20 di- and tri-methyltransferase highly expressed in the prefrontal cortex (PFC) (48). However, the specific biological function of KMT5B in the brain and its connection to autism are not well understood. In another recent study, researchers investigated the effects of Kmt5b deficiency in the PFC on behavior, synaptic transmission, and molecular mechanisms (48). Mice with Kmt5b deficiency in the PFC exhibited social deficits, a hallmark of autism, without affecting other behaviors. Additionally, Kmt5b deficiency led to impaired glutamatergic synaptic transmission in the PFC, accompanied by reduced expression of glutamate receptor subunits and associated proteins. The reduction of H4K20me2 due to Kmt5b deficiency hindered 53BP1-mediated DNA repair, resulting in increased p53 expression and upregulation of the gene Ddit4 (Redd1), which is linked to synaptic impairment (48). RNA- sequencing data revealed that Kmt5b deficiency upregulated genes involved in cellular stress response and ubiquitin- dependent protein degradation. The findings of this study highlighted the critical role of Kmt5b in the PFC and suggest that its deficiency may contribute to autistic phenotypes through synaptic dysfunction and transcriptional dysregulation (48).

SCN2A deficiency: Microglia, the brain's immune cells, play a crucial role in regulating brain development and homeostasis. Recent genetic studies have identified SCN2A deficiency as a leading cause of ASD and intellectual disability (49). A mouse model with Scn2a deficiency shows behavioral and neuronal abnormalities, with microglia playing a role in synaptic pruning (49). In humans, a cerebral organoid model with an SCN2A mutation also shows increased synaptic elimination by microglia. This recent important study highlights the importance of microglia in ASD models from mice to human cells (49).

Over-pruning Hypothesis: Another study presents the over-pruning hypothesis of autism, which suggests that overly aggressive synaptic pruning in infancy and early childhood may contribute to the development of autism (50). The hypothesis aims to explain the heterogeneity in the timing of ASD manifestation, including early onset, late onset, and regression. Computer simulations support this hypothesis by showing how unaffected siblings of individuals with ASD may inherit a milder version of the pathological mechanism or co-inherit risk factors without the mechanism. The hypothesis predicted that early development in ASD will initially appear typical and that sensory and motor issues will precede social difficulties (50). Emerging longitudinal studies provide some support for these predictions. This study reviews evidence supporting the over-pruning hypothesis, its relation to other theories, and its implications for understanding the broader autism phenotype. The hypothesis integrates data from various disciplines, including behavioral studies, neuroscience, genetics, and interventions (50).

WDR62-deficiency: Abnormal brain size is linked to a higher incidence of autism spectrum disorder (ASD) in children (51). Genetic studies have identified mutations in the WD repeat domain 62 (WDR62) gene as a factor in ASD (51). Recent research demonstrated that mice lacking Wdr62 showed reduced brain size, learning and memory

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deficits, and ASD-like behaviors (51). Interestingly, mice with Wdr62 depletion in mature neurons had normal brain size but displayed abnormal social interactions and repetitive behaviors (51). WDR62 played a role in regulating dendritic spine formation and synaptic transmission in brain cells. Treatment with retinoic acid improved ASD-like behaviors in mice with WDR62 deficiency by modulating the expression of ASD and synaptic genes. These findings offer insights into the connection between WDR62 gene mutations and ASD, which could inform better diagnosis and treatment strategies for ASD (51).

Discussion

Autism Spectrum Disorder (ASD) affects about 1% of the global population and is characterized by social interaction challenges, communication difficulties, repetitive behaviors, and focused interests. The causes of autism are largely unknown and heterozygous, leading to suboptimal care for affected individuals. To gain a better understanding of autism, studying postmortem brain tissue is of upmost importance. Studying brain tissue directly is essential because the pediatric brain is the primary organ affected by autism. It provides insights into cellular organization, connectivity, neurotransmitter systems, and brain plasticity, which are key to understanding the condition's development and potential treatments. Brain tissue research allows for histological analysis to identify neural network abnormalities, gene expression studies to understand genetic regulation in the autistic brain, and biochemical analysis to uncover changes in brain biochemistry. These studies offer valuable information on the biological basis of autism and potential treatment targets. However, researchers face challenges such as limited availability of brain tissue for study and the lack of comprehensive medical information about donors. Overcoming these challenges is crucial to advancing our understanding of autism and taking all neurochemical findings in various studies into account. In recent years, research efforts concentrate on pathological synaptic formation as the key driver of pathogenesis in autism spectrum disorders.

Synaptogenesis refers to the formation or creation of new synapses on a nerve cell. Synaptogenesis, along with synapse elimination, is the basis for the lifelong plasticity of the brain. The majority of nerve cells or neurons develop prenatally through cell division and subsequent migration. Synaptogenesis is particularly dominant in the last third of pregnancy and in the postnatal phase. At birth, humans already have 100 billion neurons. These neurons establish connections to each other through synapses, initially creating many more synapses than are actually needed. This is followed by an experience-dependent elimination of synapses. Synapse formation and elimination reach their peak at different times, depending on the brain region. For example, the peak of synapse formation in the visual cortex occurs in the first year of life. The frontal cortex, responsible for action planning among other functions, only adequately forms synapses during the preschool years, and this process can continue into adolescence. Recent studies have evaluated a dysbalance between excitatory and inhibitory synapses that are the key driver for autistic development (37,42,46). Nevertheless, there are many different additional findings in autism like a low Ig-F1 production in oligodendrocytes in the corpus callosum, leading to a slowing of PI3K/AKT chain activation of myelinization (52). Moreover, loss of protein tyrosine phosphatase receptor delta (Ptprd), mutations of Neuroligin-3-R451C, a reduced number of Chandelier cells and defects of the syntabulin-mediated synaptic cargo transport were described in different studies (39,41,43,45,49,51,53-55). Other studies revealed synaptic abnormalities with microglial Tmem59-deficiency, KMT5b deficiency in prefrontal cortex, SCN2A deficiency and WDR62 deficiency (43,48,49,51). Recent studies focus on an over-pruning hypothesis, abnormal changes in metabotropic glutamate receptor (mGluR) signaling and CHD8-gene loss on genome organization (44,47,50). In conclusion, neurochemical findings in autistic patients and studies are heterogenous, whereas recent molecular research highlighted the importance of synaptic transmission formation disturbances in autistic children. Further intensive research is of great importance to develop therapeutical targets or gene therapeutical approaches for the future for these high population of autistic spectrum disorders in childhood.

References

1. Johnson CP, Myers SM. American Academy of Pediatrics Council on Children with Disabilities. Identification and evaluation of children with autism spectrum disorders. Pediatrics 120 (2007): 1183-215.
2. Myers SM, Johnson CP. American Academy of Pediatrics Council on Children with Disabilities. Management of children with autism spectrum disorders. Pediatrics 120 (2007): 1162-82.
3. Anixt JS, Ehrhardt J, Duncan A. Evidence-Based Interventions in Autism. Pediatr Clin North Am 71 (2024): 199-221.
4. Matson JL, Goldin RL. Diagnosing young children with autism. Int J Dev Neurosci 39 (2014): 44-8.
5. Gómez-Espinosa A, Moreno JC, Pérez-de la Cruz S. Assisted Robots in Therapies for Children with Autism in Early Childhood. Sensors (Basel) 24 (2024): 1503.
6. Bruinsma Y, Koegel RL, Koegel LK. Joint attention and children with autism: a review of the literature. Ment Retard Dev Disabil Res Rev 10 (2004): 169-75.
7. Samanta P, Panigrahi A, Senapati LK, et al. Maladaptive

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DOI:10.26502/jppch.74050212

Behavior and Associated Factors among Young Children with Autism. Indian J Pediatr 89 (2022): 1134-1136.

8. Simpson K, Imms C, Keen D. The experience of participation: eliciting the views of children on the autism spectrum. Disabil Rehabil 44 (2022): 1700-1708.
9. Ten Hoopen LW, de Nijs PF, Slappendel G, et al. Associations between autism traits and family functioning over time in autistic and non-autistic children. Autism 27 (2023): 2035-2047.
10. Crane L, Jones L, Prosser R, et al. Parents' views and experiences of talking about autism with their children. Autism 23 (2019): 1969-1981.
11. Burnham Riosa P, Khan M, Weiss JA. Measuring therapeutic alliance in children with autism during cognitive behavior therapy. Clin Psychol Psychother 26 (2019): 761-767.
12. Luckett T, Bundy A, Roberts J. Do behavioural approaches teach children with autism to play or are they pretending? Autism 11 (2007): 365-88.
13. Williams E, Costall A, Reddy V. Children with autism experience problems with both objects and people. J Autism Dev Disord 29 (1999): 367-78.
14. Habayeb S, Inge A, Myrick Y, et al. A Multisystem Approach to Improving Autism Care. Pediatrics 152 (2023): e2022060584.
15. Enav Y, Erhard-Weiss D, Kopelman M, et al. A non randomized mentalization intervention for parents of children with autism. Autism Res 12 (2019): 1077-1086.
16. Truong DM, Mire SS, Day SX, et al. A cross-cultural comparison of a measure of parent perceptions among families of children with autism in Vietnam. Autism 27 (2023): 997-1010.
17. Bertoglio K, Hendren RL. New developments in autism. Psychiatr Clin North Am 32 (2009): 1-14.
18. Ahlqvist VH, Sjöqvist H, Dalman C, et al. Acetaminophen Use During Pregnancy and Children's Risk of Autism, ADHD, and Intellectual Disability. JAMA 331 (2024): 1205-1214.
19. Anixt JS, Ehrhardt J, Duncan A. Evidence-Based Interventions in Autism. Pediatr Clin North Am 71 (2024): 199-221.
20. Hernández-Díaz S, Straub L, Bateman BT, et al. Risk of Autism after Prenatal Topiramate, Valproate, or Lamotrigine Exposure. N Engl J Med 39 (2024): 1069-1079.
21. Moerkerke M, Daniels N, Tibermont L, et al. Chronic oxytocin administration stimulates the oxytocinergic system in children with autism. Nat Commun 15 (2024): 58.
22. Marra PM, Fiorillo L, Cervino G, et al. Dental problems in children with autism: a 5-year study. J Clin Pediatr Dent 48 (2024): 26-31.
23. Carbone PS, Stipelman CH, Villalobos ME, et al. A Comparison of Parent-Reported Severe Autism with Mild/Moderate Autism Among US Children. J Dev Behav Pediatr 45 (2024): e422-e430.
24. Gentles SJ, Ng-Cordell EC, Hunsche MC, et al. Trajectory research in children with an autism diagnosis: A scoping review. Autism 28 (2024): 540-564.
25. Kotagal S, Malow B, Spruyt K, et al. Melatonin use in managing insomnia in children with autism and other neurogenetic disorders - An assessment by the international pediatric sleep association (IPSA). Sleep Med 119 (2024): 222-228.
26. Hrnciarova J, Kubelkova K, Bostik V, et al. Modulation of Gut Microbiome and Autism Symptoms of ASD Children Supplemented with Biological Response Modifier: A Randomized, Double-Blinded, Placebo-Controlled Pilot Study. Nutrients 16 (2024): 1988.
27. Manning C. Visual processing and decision-making in autism and dyslexia: Insights from cross-syndrome approaches. Q J Exp Psychol (Hove) 77 (2024): 1937-1948.
28. Lee JD, Terol AK, Yoon CD, et al. Parent-to-parent support among parents of children with autism: A review of the literature. Autism 28 (2024): 263-275.
29. Yoon N, Kim S, Oh MR, et al. Intrinsic network abnormalities in children with autism spectrum disorder: an independent component analysis. Brain Imaging Behav 18 (2024): 430-443.
30. Lisk C, Mische Lawson L, Sugiura B, et al. Exploring Play Interactions of Children with Autism Spectrum Disorders and Their Pets. OTJR (Thorofare N J) 44 (2024): 179-186.
31. Pang RCC, Ho MSH, Wong PWC. A Review of the Literature on the Multiple Forms of Stigmatization of Caregivers of Children with Autism Among Ethnic Minority Groups. J Racial Ethn Health Disparities 11 (2024): 545-559.
32. Kovacheva E, Gevezova M, Maes M, et al. Mast Cells in Autism Spectrum Disorder-The Enigma to Be Solved? Int J Mol Sci 25 (2024): 2651.
33. Fatemi SH, Eschenlauer A, Aman J, et al. Quantitative proteomics of dorsolateral prefrontal cortex reveals an early pattern of synaptic dysmaturation in children with idiopathic autism. Cereb Cortex 34 (2024): 161-171.

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DOI:10.26502/jppch.74050212

34. Rexrode LE, Hartley J, Showmaker KC, et al. Molecular profiling of the hippocampus of children with autism spectrum disorder. Mol Psychiatry 29 (2024): 1968-1979.

35. Liu QQ, Mi J, Du YY, et al. Lotusine ameliorates propionic acid-induced autism spectrum disorder-like behavior in mice by activating D1 dopamine receptor in medial prefrontal cortex. Phytother Res 38 (2024): 1089-1103.

36. Wang L, Mirabella VR, Dai R, et al. Analyses of the autism-associated neuroligin- 3 R451C mutation in human neurons reveal a gain-of-function synaptic mechanism. Mol Psychiatry 29 (2024): 1620-1635.

37. Vakilzadeh G, Maseko BC, Bartely TD, et al. Increased number of excitatory synapsis and decreased number of inhibitory synapsis in the prefrontal cortex in autism. Cereb Cortex 34 (2024): 121-128.

38. Roh SH, Mendez-Vazquez H, Sathler MF, et al. Prenatal exposure to valproic acid reduces synaptic δ-catenin levels and disrupts ultrasonic vocalization in neonates. Neuropharmacology 253 (2024): 109963.

39. Cortés BI, Meza RC, Ancatén-González C, et al. Loss of protein tyrosine phosphatase receptor delta PTPRD increases the number of cortical neurons, impairs synaptic function and induces autistic-like behaviors in adult mice. Biol Res 57 (2024): 40.

40. Liu QQ, Mi J, Du YY, et al. Lotusine ameliorates propionic acid-induced autism spectrum disorder-like behavior in mice by activating D1 dopamine receptor in medial prefrontal cortex. Phytother Res 38 (2024): 1089-1103.

41. Hong T, McBride E, Dufour BD, et al. Synaptic boutons are smaller in chandelier cell cartridges in autism. PLoS One 18 (2023): e0281477.

42. Reis SL, Monteiro P. From synaptic dysfunction to atypical emotional processing in autism. FEBS Lett 598 (2024): 269-282.

43. Meng J, Han L, Zheng N, et al. Microglial Tmem59 Deficiency Impairs Phagocytosis of Synapse and Leads to Autism-Like Behaviors in Mice. J Neurosci 42 (2022): 4958-4979.

44. Shi X, Lu C, Corman A, et al. Heterozygous deletion of the autism-associated gene CHD8 impairs synaptic function through widespread changes in gene expression and chromatin compaction. Am J Hum Genet 110 (2023): 1750-1768.

45. Xiong GJ, Cheng XT, Sun T, et al. Defects in syntabulin-mediated synaptic cargo transport associate with autism-like synaptic dysfunction and social behavioral traits. Mol Psychiatry 26 (2021): 1472-1490.

46. Bourgeron T. The possible interplay of synaptic and clock genes in autism spectrum disorders. Cold Spring Harb Symp Quant Biol 72 (2007): 645-54.

47. Edfawy M, Guedes JR, Pereira MI, et al. Abnormal mGluR-mediated synaptic plasticity and autism-like behaviours in Gprasp2 mutant mice. Nat Commun 10 (2019): 1431.

48. Wang ZJ, Rein B, Zhong P, et al. Autism risk gene KMT5B deficiency in prefrontal cortex induces synaptic dysfunction and social deficits via alterations of DNA repair and gene transcription. Neuropsychopharmacology 46 (2021): 1617-1626.

49. Wu J, Zhang J, Chen X, et al. Microglial over-pruning of synapses during development in autism-associated SCN2A-deficient mice and human cerebral organoids. Mol Psychiatry 29 (2024): 2424-2437.

50. Thomas MS, Davis R, Karmiloff-Smith A, et al. The over-pruning hypothesis of autism. Dev Sci 19 (2016): 284-305.

51. Xu D, Zhi Y, Liu X, et al. WDR62-deficiency Causes Autism- like Behaviors Independent of Microcephaly in Mice. Neurosci Bull 39 (2023): 1333-1347.

52. Velmeshev D, Schirmer L, Jung D, et al. Single-cell genomics identifies cell type-specific molecular changes in autism. Science 364 (2019): 685-689.

53. Sharna SS, Balasuriya GK, Hosie S, et al. Altered Caecal Neuroimmune Interactions in the Neuroligin-3R451CMouse Model of Autism. Front Cell Neurosci 14 (2020): 85.

54. Dingwall R, May C, Letschert J, et al. Attenuated responses to attention- modulating drugs in the neuroligin-3R451C mouse model of autism. J Neurochem 168 (2024): 2285-2302.

55. Li S, May C, Pang TY, et al. Mice with an autism-associated R451C mutation in neuroligin-3 show intact attention orienting but atypical responses to methylphenidate and atomoxetine in the mouse-Posner task. Psychopharmacology (Berl) 241 (2024): 555-567.